Preparation of methoxy-substituted para-benzoquinones

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Abstract: A facile route to 5-substituted 2-methoxy-para-benzoquinones from 5-substituted 2-phenols is described. The synthetic route is also used to prepare steroid-para-benzoquinone hybrids. Cyclovoltammographic and UV-spectroscopic behavior of methoxy-substituted para-benzoquinones are touched upon as well.

Introduction:

Quinones are distributed widely in living organisms. Some of the more familiar ones are plastoquinone and phylloquinone, both quinones needed in photosynthesis, and ubiquinone, also known as coenzyme Q10, which participates in the aerobic cellular respiration. All of the above are substituted *p*-benzoquinones. Anthracyclines can be viewed as having a quinoid group. A number of members of this family such as daunorubicin and doxorubicin are used in cancer chemotherapy. Also menadione (2-methylnaphtho-1,4-quinone), which is sold as a nutritional supplement as a vitamin K mimic, has been viewed as a potential drug for prostate cancer treatment (Jamison 2001). Overall, in 1991, quinones constituted the second largest group of cytotoxins used in chemical cancer therapy, after specifically alkylating agents such as mustards (O'Brien 1991), with about 1500 quinones already tested in 1974 (Driscoll et al. 1974). Quinones have a number of actions in the body. In strongly dividing cells, their most influential action is the interaction with DNA material which may lead to DNA damage or to changed DNA resulting in cell mutations (O'Brien 1991). In non-dividing cells or in cells at rest the main action of the quinones is a possible alkylation of proteins through their thiol or amino groups (O'Brien 1991). Most important, though, is the reduction of the quinones to the respective semiquinone radicals by reductase. The semiquinone radicals in turn reduce oxygen to superoxide radicals and reform as quinones. The superoxide radicals, which are usually scavenged in the body by the enzyme superoxide dismutase, are very toxic and lead among others the oxidation of cystein residues to cystine in proteins and the oxidation of glutathione (GSH) to glutathione disulfide (GSSG) (O'Brien 1991).

It has been found that the protein NAD(P)H:quinone oxidoreductase (QR1) is overexpressed in many human solid tumours such as adrenal, thyroid, breast, ovarian, colon, and non-small-cell lung cancer (Siegel and Ross 2000). This enzyme poses a possible target for quinone drugs. Recently, the crystal structure of the protein complexed to different synthetic quinones has been published (Faig et al. 2001). Among other details, it had been shown that the protein is relatively flexible to ligand differently substituted quinones, which may bind to QR1 in different orientations.

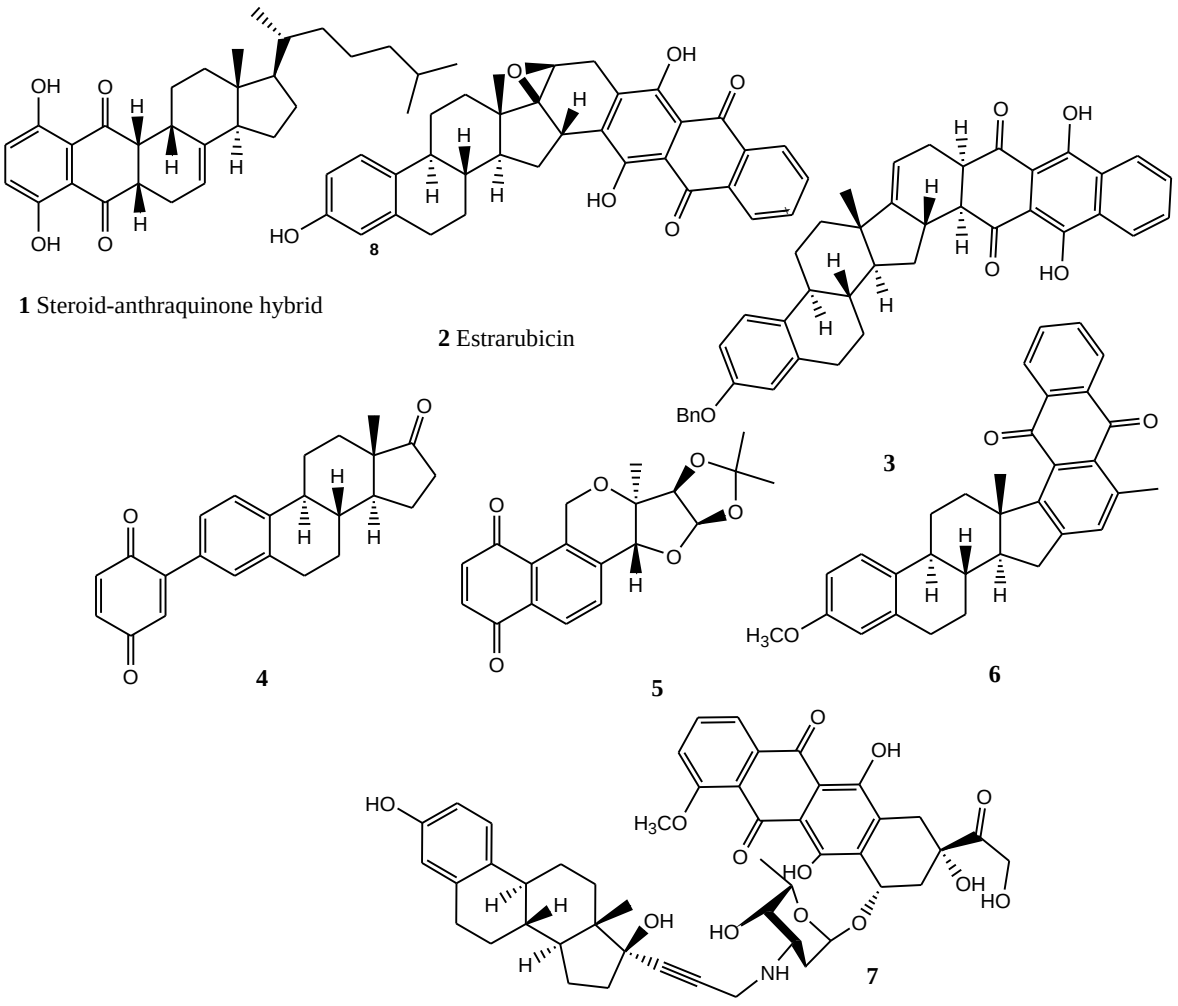


Figure 1. Overview of steroid derived quinone hybrids and steroid mimic quinone hybrids from the literature.

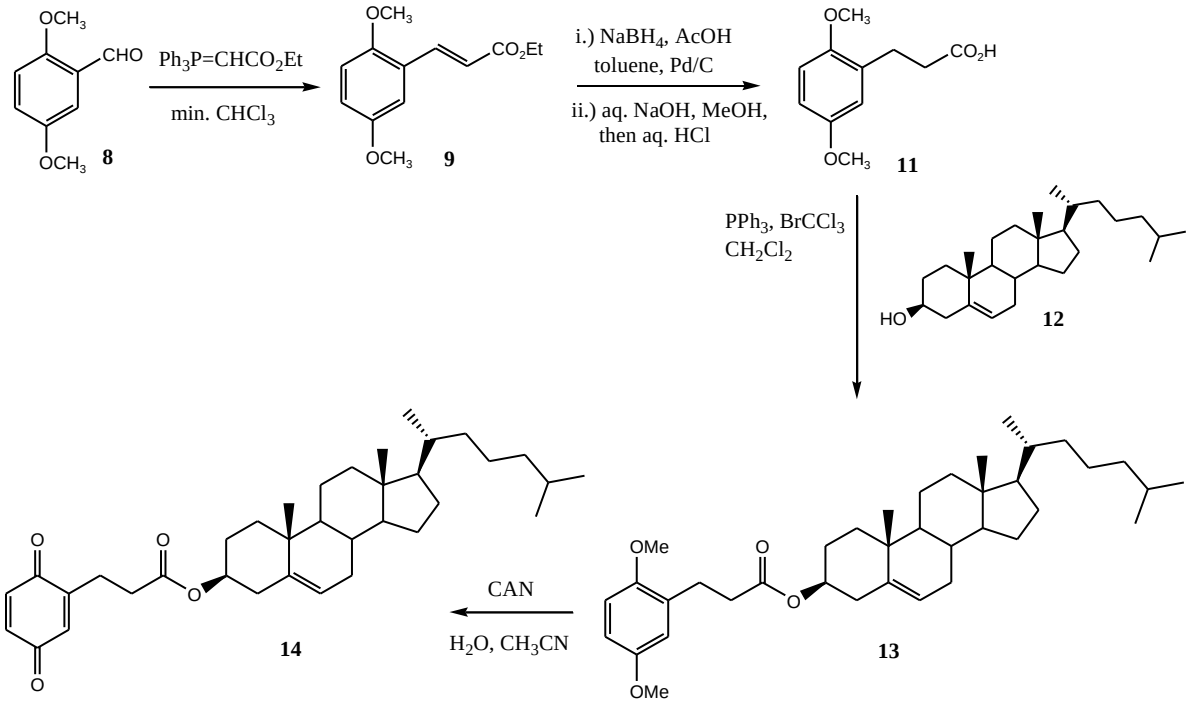
With the known cancer activity of anthracyclines and the idea of utilizing steroidal moieties and drug delivery systems, anthracyline-steroid hybrids (Dao *et al.*, 2012) such as **7** (Figure 1) (Hartman *et al.*, 1990) were synthesized and their biological activity was investigated. These

studies were extended to dihydroxyarenoquinone containing steroids such as **1**, **2** and **3** (de Riccardis *et al.*, 1997; de Riccardis *et al.*, 1998), then to quinoid containing steroid **4** (Fujiwara *et al.*, 2011) and steroidal mimic **5** (Kaliappan & Ravikumar, 2005). The Thiemann group had communicated the annelated steroidal anthraquinone **6** previously (Ribeiro Morais et al. 2005). Against this background, the authors have studied simple ways to synthesize substituted quinones, also with the aim of linking quinoid structures to steroidal bodies. Also, the authors have been interested to study the electrochemical response of *p*-benzoquinones. In continuation of our work on alkyl substituted quinones (AlAzani 2015), we present here an easy access to methoxy-substituted 1,4-benzoquinones that can also be linked to steroidal moieties.

Results and Discussion

a.) Synthesis

In recent times, we have developed a short route to amidoethylquinones (Al Soom 2016a, AlAzani 2015), alkylquinones and their derivatives. The route starts from commercially available 2,5-dimethoxybenzaldehyde **8** which is converted to cinnamate **9**. This is hydrogenated to phenylpropionate **10** ($NaBH_4$, AcOH, Pd/C) (Russo 2011, al Soom 2016b) and hydrolyzed to phenylpropionic acid **11**. The phenylpropionic acid is converted to either an amide or an ester by a modified Appel reaction ($BrCCl_3$, PPh_3, CH_2Cl_2) (AlAzani 2016) which links the quinone precursor to a second moiety of interest, either as a potential drug delivery system or for other purposes. In the last step the 1,4-dimethoxy-substituted phenyl group is converted to the *p*-quinoid in a conventional way using cerium ammonium nitrate (CAN). A typical example of such an approach is shown in Scheme 1, where the quinoid moiety is connected to cholesterol (**12**) at C3 via an ester function to give **14** (Al Soom 2016a).



Scheme 1. Overall reaction sequence to 3-cholesteryl 1,4-quinon-2-ylpropionate **14**

Here, we had wanted to explore a similar approach starting out with 3-hydroxy-4-methoxybenzaldehyde with the idea of finally converting the 3-hydroxy-4-methoxyphenyl group to an *ortho*-quinone system. 3-Hydroxy-4-methoxybenzaldehyde (**25**) could either be protected as its *O*-benzyl derivative **26** and then converted by Wittig reaction to the corresponding cinnamate **27** or reacted directly by Wittig reaction to the hydroxy-substituted cinnamate **32**. Reductive hydrogenation ($NaBH_4$, AcOH, Pd/C) of both the benzyloxy-substituted cinnamate and the hydroxyl-substituted cinnamate provides, after hydrolysis, 3-hydroxy-4-methoxyphenylpropionic acid (**31**). This can be esterified or amidated to compounds **15**.

When, the 3-hydroxy-4-methoxyphenylpropionamides **15** and derivatives were treated with CAN in H_2O-AcCN, methoxyquinonylpropionamides **16** were produced (Table 1), not the expected *ortho*-quinones.

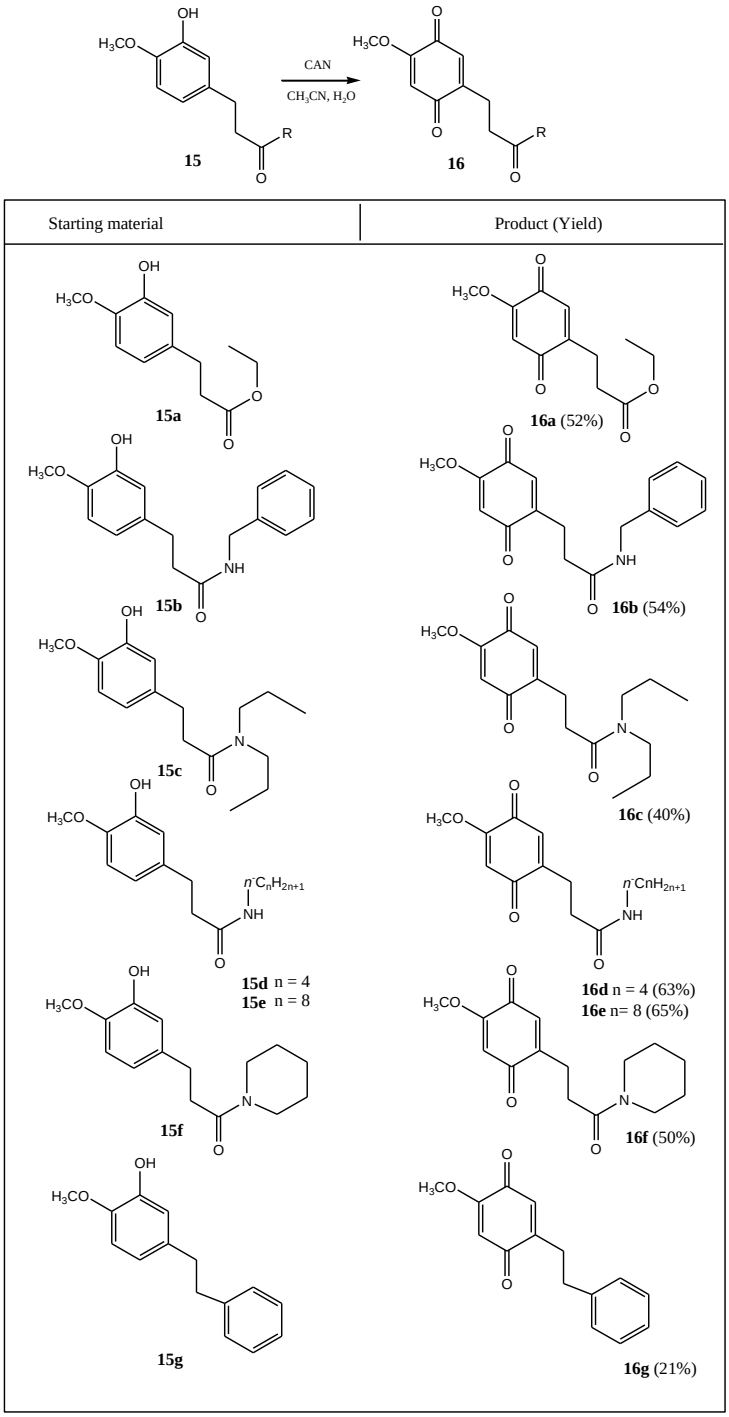
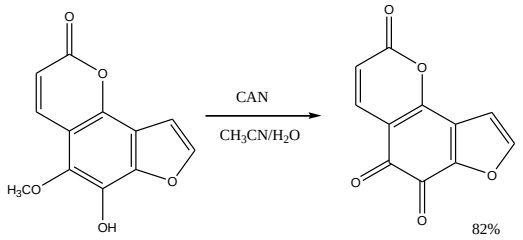


Table 1. Conversion of 3-hydroxy-4-methoxyphenylpropionate and 3-hydroxy-4-methoxyphenylpropionamides **15** to alkoxycarbonylethyl-methoxy-quinone and amidoethyl-methoxy-quinones **16** with cerium ammonium nitrate (CAN) in a mixture of CH_3CN and H_2O.

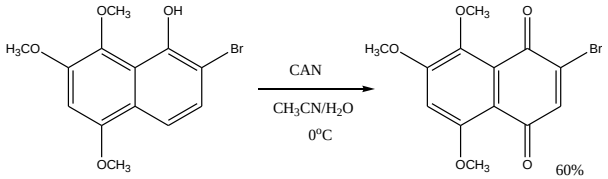
The conversion of the hydroxyl-methoxyarene to the methoxyquinone system is of interest and not trivial as, as said above, it could have been envisaged that an *ortho*-quinone (minus methoxy group) would form as there is some precedence for this as in the synthesis of isopsoralenquinone **18** (Scheme 2) (Reed and Moore 1988).



17 **18**

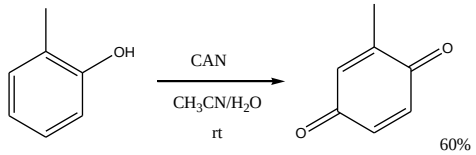
Scheme 2. Synthesis of isopsoralenquinone (**18**) by CAN oxidation of **17** (Reed and Moore 1988).

There are some examples, however, where an oxo group is introduced *para* to a hydroxy- or methoxy group upon reaction with CAN, if the *para*-position is available. Examples are given in Schemes 3, 4 and 5.



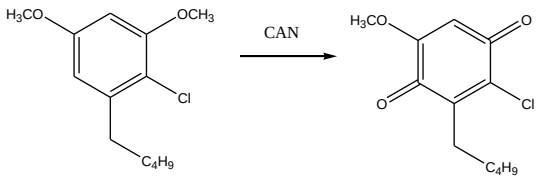
19 **20**

Scheme 3. Oxidation of bromonaphthol **19** to naphthoquinone **20** with CAN (Wu et el. 2011)



21 **22**

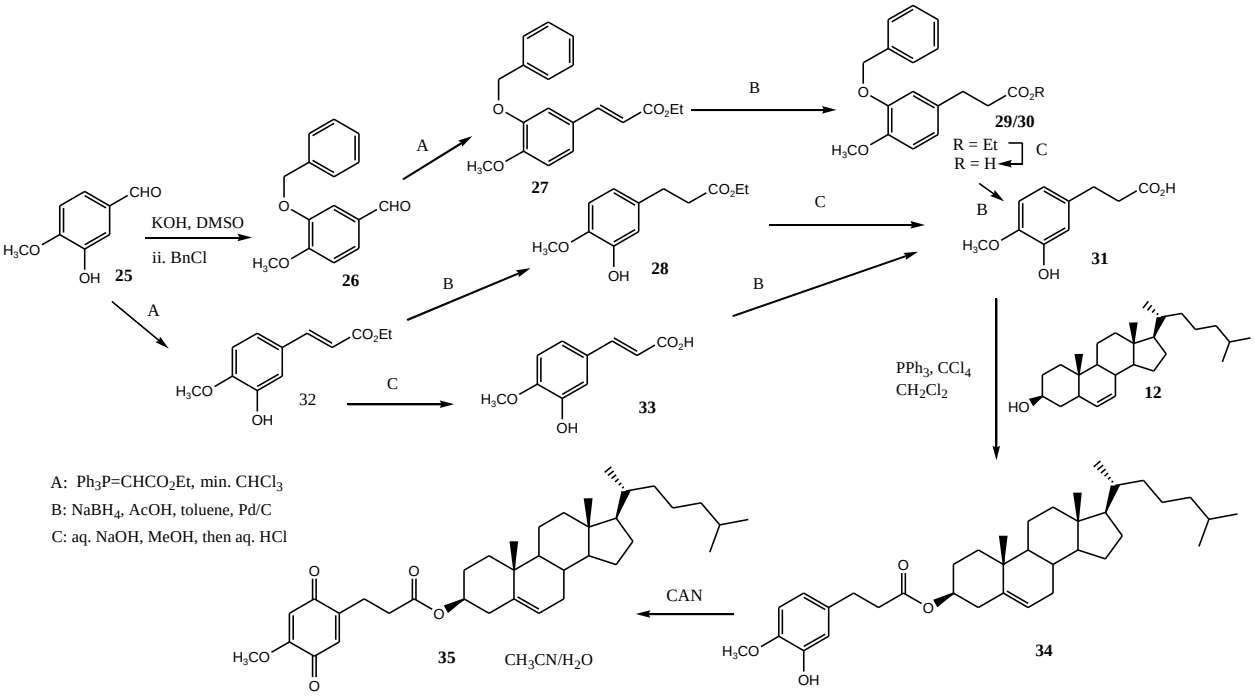
Scheme 4. Oxidation of 2-methylphenol (**21**) to 2-methyl-*p*-benzoquinone (**22**) with CAN (Rao et al. 1985)



23 **24**

Scheme 5. Oxidation to chloromethoxybenzoquinone (**24**) with CAN (Spyroudis 2000, Bruner et al. 1995)

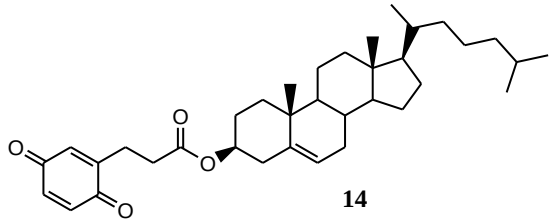
Scheme 5 shows a typical example, where an oxo group is introduced by CAN into the 1,4-position to a methoxy group to give a *p*-quinone is the chloro-methoxy-substituted arene **23**, which is transformed to **24** (Spyroudis 2000, Bruner et al. 1995). The direct oxidation of phenols to *para*-quinones can also be achieved with salcomine/O_2 (Podlesny and Kozlowski 2012) and with O_2 itself in the presence of a base (Danheiser et al. 1992) such as TBAF or KOBu^t.



Scheme 6. Overall reaction sequence to cholesteryl 5-methoxy-1,4-quinon-2-ylpropionate (**35**) with different synthetic routes to 3-hydroxy-4-methoxyphenylpropionic acid. (**31**)

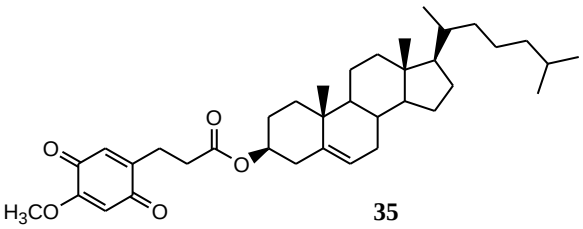
The conversion of 3-hydroxy-4-methoxyarenes to methoxyquinones was also used to link a methoxyquinone to cholesterol as shown in Scheme 6. In all, the transformation from 3-hydroxy-4-methoxyphenylpropionamides and 3-hydroxy-4-methoxyphenylpropionates to the corresponding methoxyquinones, pursued in this contribution, is worth a more comprehensive study.

b.) Spectroscopic analysis



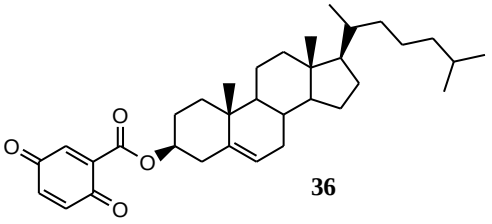
14

CH_2Cl_2: λ = 310 nm (ε = 642 $mol^{-1}cm^{-1}$); λ = 250 nm (ε = 22570 $mol^{-1}cm^{-1}$)
CH_3CN:λ = 305 nm (ε = 646 $mol^{-1}cm^{-1}$); λ = 250 nm (ε = 14950 $mol^{-1}cm^{-1}$)



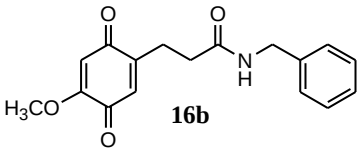
35

CH_2Cl_2: λ = 360 nm (ε = 595 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 12500 $mol^{-1}cm^{-1}$)



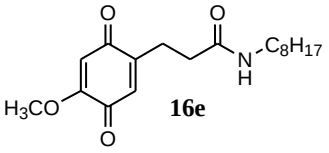
36

CH_2Cl_2: λ = 325 nm (ε = 1072 $mol^{-1}cm^{-1}$); cnd
CH_3CN:λ = 325 nm (ε = 1025 $mol^{-1}cm^{-1}$); λ = 245 nm (ε = 17710 $mol^{-1}cm^{-1}$)



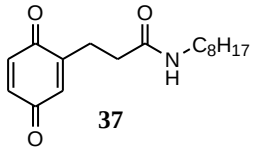
16b

CH_2Cl_2: λ = 351 nm (ε = 220 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 5665 $mol^{-1}cm^{-1}$)
CH_3CN:λ = 351 nm (ε = 490 $mol^{-1}cm^{-1}$); λ = 260 nm (ε = 8150 $mol^{-1}cm^{-1}$)



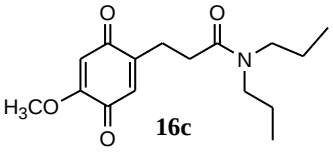
16e

CH_2Cl_2: λ = 355 nm (ε = 598 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 15020 $mol^{-1}cm^{-1}$)



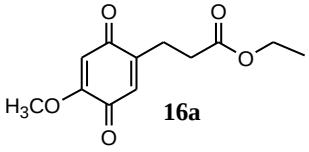
37

CH_3CN:λ = 325 nm (ε = 1500 $mol^{-1}cm^{-1}$); cnd



16c

CH_2Cl_2: λ = 355 nm (ε = 547 $mol^{-1}cm^{-1}$); λ = 265 nm (ε = 13730 $mol^{-1}cm^{-1}$)
CH_3CN:λ = 351 nm (ε = 718 $mol^{-1}cm^{-1}$); λ = 260 nm (ε = 25480 $mol^{-1}cm^{-1}$)



16a

CH_3CN: λ = 360 nm (ε = 595 $mol^{-1}cm^{-1}$); λ = 260 nm (ε = 15100 $mol^{-1}cm^{-1}$)

Table 2. UV-VIS absorption data for selected quinones.

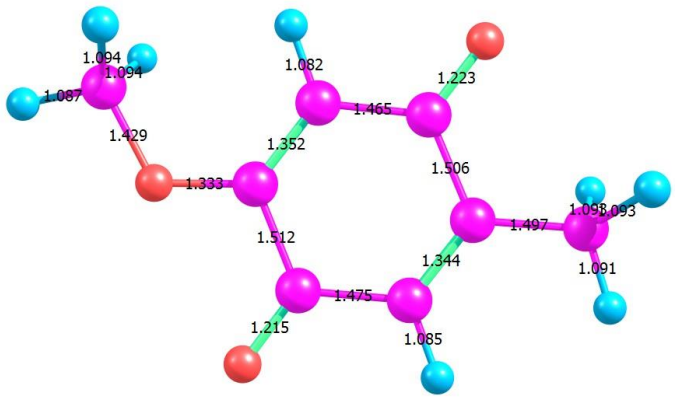
The UV-VIS spectra of the acquired quinones were measured in CH_2Cl_2 and CH_3CN (Table 2). No appreciable solvent effect was noted, however. The isolated alkyl-substituted quinones show an intense absorption at λ = 245 - 250 nm and a weaker absorption band at λ = 305 - 325 nm (see

Table 5), while the carboxyl-substituted quinone xx absorbs at λ = 245 nm and λ = 325 nm. The methoxy substituted quinones display an intense absorption at λ = 265 nm and a weaker absorption band at λ = 350 - 360 nm, meaning that both absorption bands are shifted towards lower energy versus the isolated quinone systems.

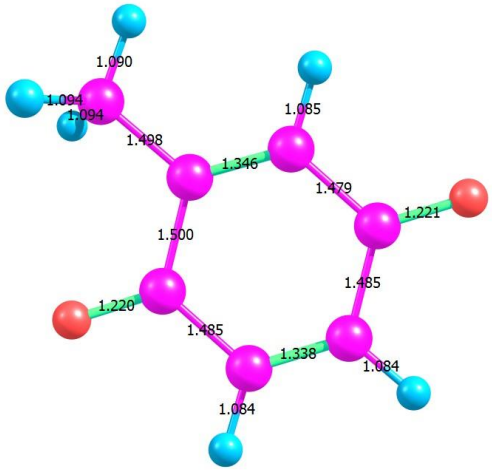
According to the literature, both absorptions that were observed are related to π-π* transitions. n-π* Transitions have been reported to be very weak and at longer wavelengths (400-500 nm and 650 nm, respectively) (Orlando et al. 1968, Kuboyama 1962). These were not specifically looked for in our case. Structural and orbital calculations of 2-methoxy-5-methyl-1,4-benzoquinone and 2-methyl-1,4-benzoquinone indicated a bathochromic shift of the 2-methoxy-5-alkyl substituted benzoquinone versus the 2-alkyl substituted benzoquinone of about $\Delta\lambda$ = 15 nm, which was also found experimentally, without reproducing the exact λ_{max} of the electronic transitions (Figure 2).

Figure 2.

Figure 2a. Optimized Structures of 2-methoxy-5-methyl-1,4-benzoquinone and 2-methylbenzo-1,4-quinone: (B3LYP/6-311+G(d,p):



2-Methoxy-5-methyl-1,4-benzoquinone

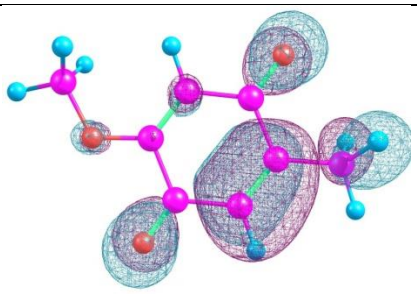
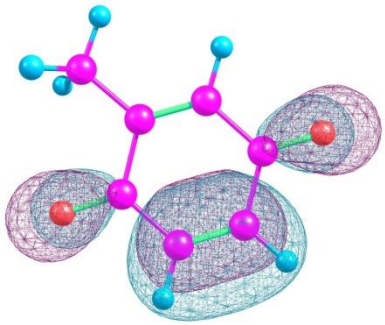
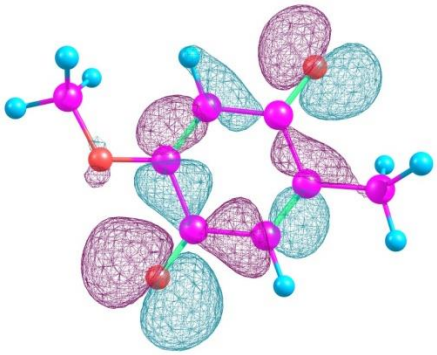
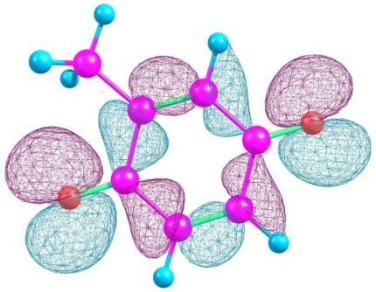


2-Methyl-1,4-benzoquinone

Table 3. Orbital Energies (eV):

	HOMO-3	HOMO-2	HOMO-1	HOMO	LUMO
2-methoxy-5-methyl-BQ	-8.17	-7.77	-7.50	-7.38	-3.45
2-methyl-BQ	-8.63	-8.20	-7.95	-7.65	-3.78

Figure 2b. Orbital Isosurfaces:

	2-Methoxy-5-methyl-1,4-benzoquinone:	2-Methyl-1,4-benzoquinone:
HOMO-3		
HOMO-2		

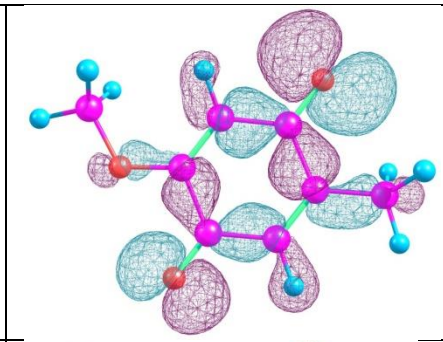
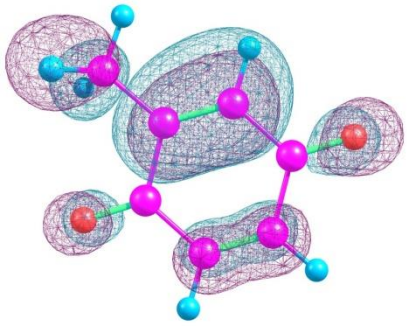
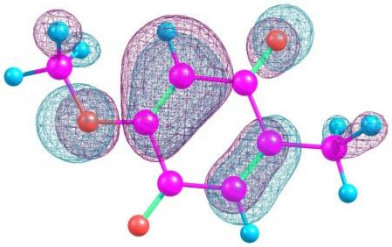
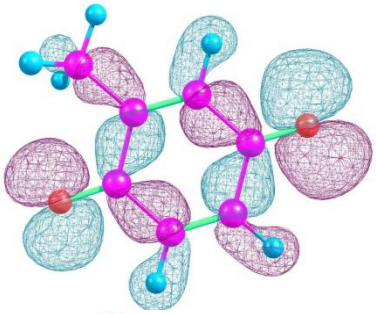
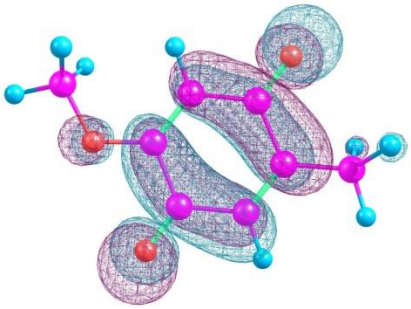
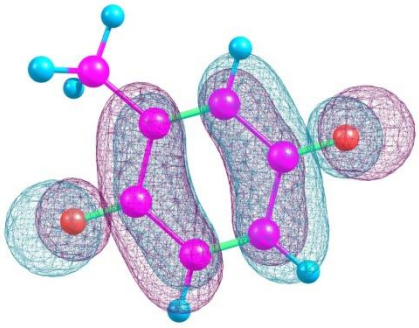
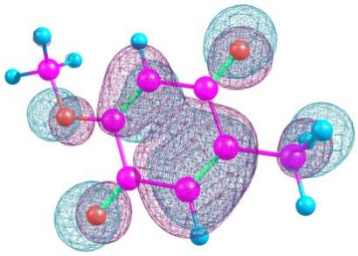
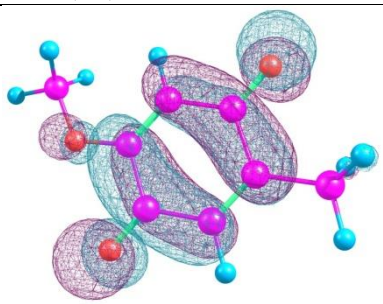
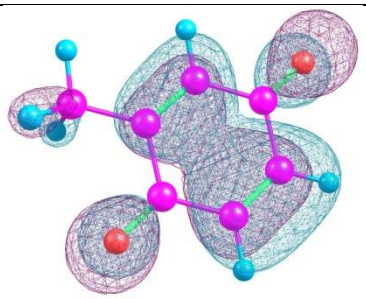
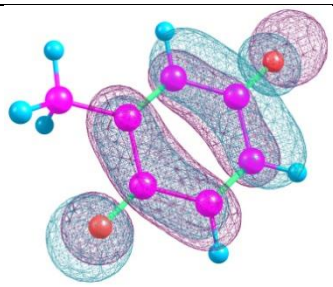
HOMO-1		
HOMO		
LUMO		

Figure 2c. Electronic Spectra: (CAM-B3LYP/6-311+G(d,p):

	λ_{max}	Contributions	NTO (From)	NTO (To)
2-methoxy-5-methyl-BQ	247 nm	Major (0.67) HOMO-3→LUMO Minor (0.17): HOMO→LUMO		

2-methyl-BQ	236 nm	Major (0.63) HOMO-3→ LUMO Minor (0.29) HOMO→ LUMO		

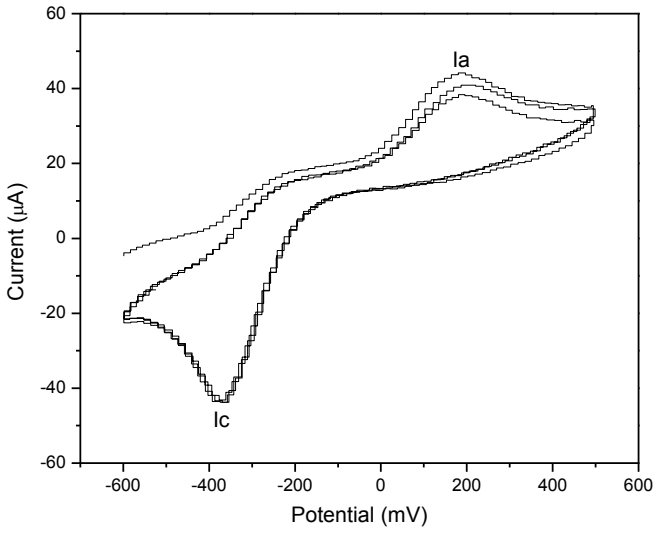


Figure 3. Typical cyclic voltammograms (3 cycles) of 1 mM (compound **16d**) in MeCN: H_2O (95:5) containing 0.05 M Bu_4NPF_6 and 0.05 M acetic acid as supporting electrolyte, on glassy carbon electrode (I.d. 3 mm) as a working electrode. Initial potential = -0.6 V, final potential = 0.5 V, scan rate = 100 mV/s, calomel electrode as a reference electrode and platinum wire (o.d. 1.1 mm) as an auxiliary electrode.

Also, in continuation of our studies of the electrochemical behavior of substituted quinones (AlAzani 2013, Gomez-Berenguer 2012), we have subjected methoxyquinone **16d** to a cyclovoltammographic study in acetonitrile/H_2O (95:5) (Figure 3).

Conclusion and future target:

Here, it could be shown that alkylated 3-hydroxy-4-methoxyarenes can be oxidized to methoxy substituted quinones. This strategy was also used to prepare quinone-steroidal hybrids (eg., quinone-cholesterol hybrids). In the UV spectra, the methoxy-substituted alkylquinones exhibit a slight bathochromic shift as compared to alkylquinones themselves. Future targets remain

estradiol-quinone hybrids of type **38** and **39** (Figure 4). A corresponding estradiol bound to a *p*-quinoid moiety through C17(OH) via an ester linkage has already been synthesized along the synthetic lines shown above.

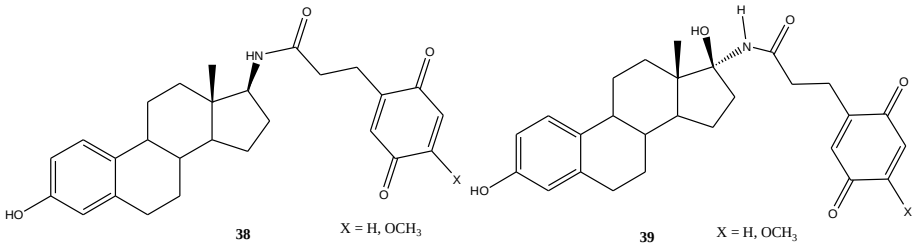


Figure 4. Future targets of this work

Experimental:

General: Melting points were measured on a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 NMR (^{1}H at 395.7 MHz, ^{13}C at 100.5 MHz) and a Varian 200 MHz NMR spectrometer (^{1}H at 200.0 MHz, ^{13}C at 50.3 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer. CHN-analysis was performed on a LECO TruSpec Micro instrument. Column chromatography was carried out on silica gel (60 A, 230 – 400 mesh, Sigma-Aldrich).UV-VIS spectroscopy was carried out on a Cary-50 instrument. As solvents for the UV-VIS spectroscopic measurements, CH_3CN (190 far UV, super purity, Romil Chemicals) and CH_2Cl_2 (Aldrich) were used. $NaBH_4$ (Fisher Scientific), ammonium cerium nitrate (CAN, Fisher Scientific), ethyl bromoacetate (Ventron), bromotrichloromethane ($BrCCl_3$, Aldrich), tetrachlorocarbon (CCl_4, Riedel-de-Haën), 2,5-dimethoxybenzaldehyde (**8**), 3-hydroxy-4-methoxybenzaldehyde (**25**) (Aldrich), triphenylphosphine (PPh_3, Aldrich), Pd/C (Aldrich, 5 wt%, 205680) were acquired commercially.

3-Cholesteryl 3-hydroxy-4-methoxyphenylpropionate (**34**). – A solution of triphenylphosphine (PPh_3, 854 mg, 3.26 mmol) and tetrachloromethane (CCl_4, 550 mg, 3.58 mmol) in dry CH_2Cl_2 (12 mL) was stirred at reflux for 50 min. Then, 3-hydroxy-4-methoxyphenylpropionic acid (**31**, 535 mg, 2.73 mmol) was added, and the mixture was stirred at reflux for 1h. Then, cholesterol (**12**,

1.585 g, 4.1 mmol) was added, and the resulting mixture was stirred at reflux for 14h. The mixture was subjected directly to column chromatography on silica gel (eluant: CH_2Cl_2) to give **34** (960 mg) as a colorless solid, mp. 130 ºC; ν_{max} (KBr/cm^{-1}) 3922 (ds, OH), 2939, 2903, 2866, 2850, 1698, 1592, 1536, 1465, 1437, 1364, 1255, 1213, 1129, 1032, 875, 801; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, CH_3), 0.84 (3H, d, ^3J = 6.0 Hz, CH_3), 0.84(5) (3H, d, ^3J = 6.4 Hz, CH_3), 0.89 (3H, d, ^3J = 6.4 Hz, CH_3), 0.92 – 2.01 (26H, m), 0.99 (3H, s, CH_3), 2.27 (2H, bd, J = 8.0 Hz), 2.54 (2H, t, ^3J = 7.6 Hz), 2.83 (2H, d, ^3J = 7.6 Hz), 3.84 (3H, s, OCH_3), 4.55 – 4.63 (1H, m), 5.34 (1H, bd, ^3J = 4.0 Hz), 5.53 (1H, bs, OH), 6.65 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 6.75 (1H, d, ^3J = 8.0 Hz), 6.76 (1H, d, ^4J = 2.0 Hz); δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3), 18.7, 19.3, 21.0, 22.6, 22.8, 23.8, 24.3, 27.7, 28.0, 28.2, 30.4, 31.8 (2C), 31.9, 35.8, 36.1(5), 36.4, 36.6, 36.9(5), 38.1, 39.5, 39.7, 42.3, 50.0, 55.9(5), 56.1, 56.6, 74.0 (CH), 110.6 (CH), 114.5 (CH), 119.6 (CH), 122.6 (CH), 133.9 (C_{quat}), 139.6 (C_{quat}), 144.9 (C_{quat}), 145.4 (C_{quat}), 172.4 (C_{quat}, CO).

Cholesteryl 5-methoxy-1,4-quinon-2-ylpropionate (**35**). – To a stirred solution of **34** (265 mg, 0.47 mmol) in a solvent mixture of CH_2Cl_2 (5 mL) and CH_3CN (10 mL) was added CAN (810 mg, 1.47 mmol) in H_2O (10 mL). The reaction mixture was stirred for 15 min. at rt. Then, H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2/ether 5:1) yielded **35** (145 mg) as a yellow-brown solid, mp. 202 ºC; ν_{max} (KBr/cm^{-1}) 2938, 2867, 1732, 1671, 1649, 1606, 1465, 1374, 1172, 980; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, s, CH_3), 0.84 (3H, d, ^3J = 6.8 Hz), 0.84(5) (3H, d, ^3J = 6.4 Hz), 0.89 (3H, d, ^3J = 6.8 Hz), 0.86 – 1.85 (24H, m), 0.99 (3H, s, CH_3), 1.92 – 2.01 (2H, m), 2.27 (2H, d, ^3J = 7.6 Hz), 2.52 (2H, t, ^3J = 7.2 Hz), 2.74 (2H, dt, ^3J = 7.2 Hz, ^4J = 0.8 Hz), 3.80 (3H, s, OCH_3), 4.55 – 4.63 (1H, m), 5.35 (1H, d, ^3J = 3.6 Hz), 5.92 (1H, s), 6.51 (1H, t, ^4J = 0.8 Hz); □$_C$ (67.8 MHz, $CDCl_3$) 11.8 (CH_3), 18.7 (CH_3), 19.3 (CH_3), 21.0, 22.5, 22.8, 23.8, 24.3, 24.6, 27.7, 28.0 (2C), 28.2, 31.8, 31.9, 32.5, 35.8, 36.1, 36.5, 36.9, 38.1, 39.5, 39.7, 42.3, 50.0, 56.1, 56.3, 56.6, 74.4 (CH), 107.7 (CH), 122.8, 131.0, 139.4, 148.5, 158.6, 171.3 (C_{quat}, CO), 182.1 (C_{quat}, CO), 187.0 (C_{quat}, CO); UV (CH_2Cl_2) λ = 360 nm (ε = 585), λ = 249.9 nm (ε = 12850).

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